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Enantioselective Synthesis of Aminodiols by Sequential Rh-Catalysed Oxyamination/Kinetic Resolution. Expanding the Substrate Scope of Amidine-Based Catalysis

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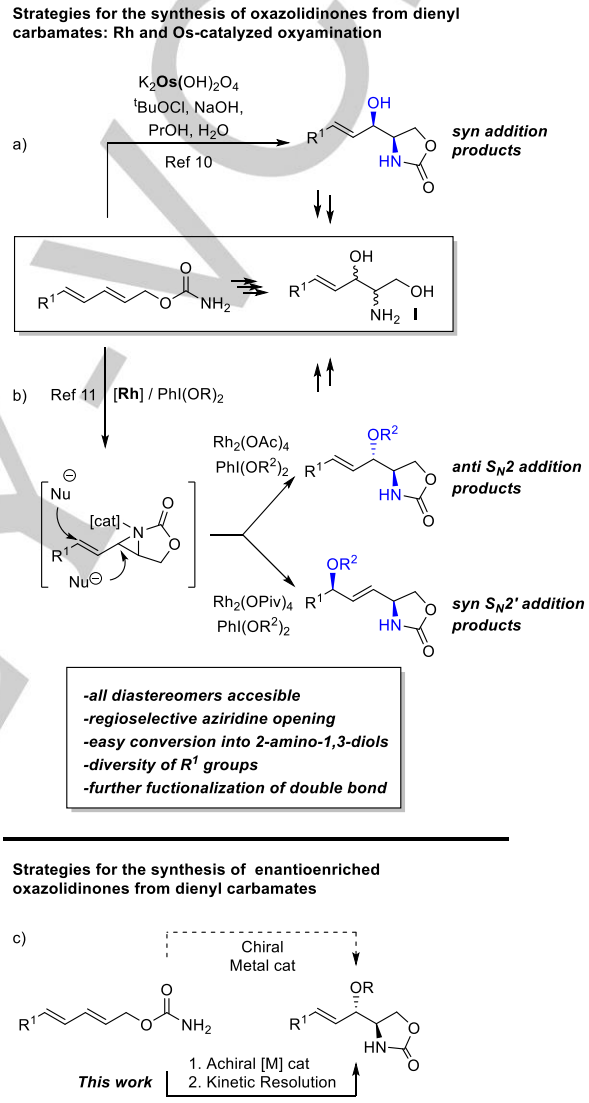
Abstract: Regio- and stereoselective oxyamination of dienes through a tandem rhodium catalysed aziridination-nucleophilic opening affords racemic oxazolidinone derivatives, which undergo a kinetic resolution acylation process using ABCs (amidine-based catalysts) achieving *s* values up to 117. This protocol was applied to the enantioselective synthesis of sphingosine.

Introduction

Vicinal amino alcohol and 2-amino-1,3-diol derivatives (**I**, Scheme 1) are common structural motifs present in nature. Relevant members of this family are sphingoid bases,[1] sphinganines and clavaminol derivatives,[2] which play important roles in physiological processes. In particular, sphingolipids, components of the cell membrane in living organisms, have been reported to be involved in cell recognition and signal transduction,[3] and show antitumor,[4] immune-modulatory,[5] and immunosuppressive activities.[6] Their syntheses commonly involve chiral pool approaches.[7]

An alternative strategy for the syntheses of vicinal amino alcohol-containing compounds relies on the transition metal-catalysed (osmiun, rhodium, palladium, copper or platinum) oxyamination of allyl carbamates.[8] However, the oxyamination of dienols to afford vinyl-aminodiols, which are interesting intermediates in the synthesis of sphingoid bases, as well as aminopolyols and amino- and iminosugars, has drawn much less attention.[9] In 2001, Donohoe and coworkers reported the oxyamination of 2,4-dien-1-yl carbamates with osmiun reagents to afford 2-amino-pent-4-en-1,3-diol derivatives (Scheme 1a).[10] Recently, we demonstrated that rhodium-catalysed intramolecular aziridination of dienyl carbamates[11] in the presence of $PhI(OR)_2$ affords vinylaziridines,[12,13] which are *in situ* opened by the OR group released after the nitrene transfer reagent formation. The regioselectivity of this process (S_N2 *versus* S_N2') was controlled by properly selecting the catalyst and the $PhI(OR)_2$ reagent (Scheme 1b).[11] Thus oxazolidinone derivatives with opposite



Scheme 1. Reported processes for the metal-catalysed oxyamination of dienyl carbamates (a, b) and strategies for the enantioselective synthesis of oxazolidinones (c).

relative configuration can be obtained from the same carbamate depending on whether an osmium or rhodium catalysts is used (Scheme 1), or modifying the configuration of the proximal double bond at the dienyl carbamate under a given catalytic system. Final hydrolysis of the oxazolidinone intermediate gave access to desired 2-amino-1,3-diol compounds. Overall, a variety of alkenyl aminodiols was accessible with high chemo-, regio-, and stereoselectivity using these procedures. The possibility of double bond functionalization or chain elongation

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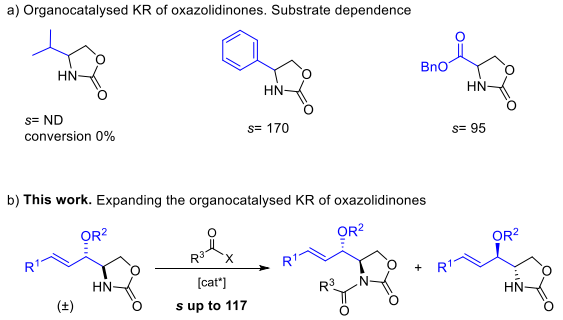


Scheme 2. Organocatalysed kinetic resolution (KR) acylation of oxazolidinones via acylation: a) reported results,[18] b) this work.

with different R^1 groups through metathesis reactions expand the synthetic application of the present methodology.

However, to the best of our knowledge, the asymmetric synthesis of vicinal amino alcohols via an enantioselective catalytic oxyamination of dienyl carbamates or via a kinetic resolution of the intermediate racemic oxazolidinones is still unexplored (Scheme 1c).[14] Here we report a tandem regio- and stereocontrolled rhodium-catalysed intramolecular aziridination/ ring-opening of 2,4-dien-1-yl carbamates with oxygen nucleophiles, followed by an organocatalysed kinetic resolution of the resulting oxazolidinones to obtain enantioenriched 4-ene-2-amino-1,3-diol derivatives (Scheme 2). The usefulness of the present methodology is illustrated by its application to the synthesis of enantioenriched sphingosine (see Scheme 5).

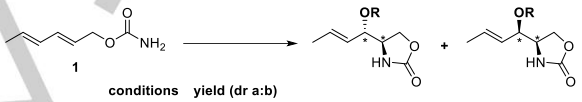
Results and Discussion

Chiral Rh(II) catalysts bearing carboxyamidate or carboxylate ligands have been widely used in asymmetric processes, providing excellent results in terms of selectivity.[15] Aiming to develop the enantioselective version of the oxyamination procedure, we initially explored the reaction of carbamate **1** (See Scheme 3) with $PhI(OPiv)_2$ in the presence of chiral dirhodium carboxyamidate catalysts $Rh_2(4S\text{-MEOX})_4(CH_3CN)_2$, $Rh_2(4R\text{-IPOX})_4(CH_3CN)_2$ and $Rh_2(4S\text{-PHOX})_4(CH_3CN)_2$.[16] However, all three catalysts afforded a complex mixture of compounds under different reaction conditions. We speculate that steric congestion at the axial reactive sites of rhodium complexes containing carboxymidate ligands could be the reason for the low catalyst activity observed. Alternatively, other rhodium(II) complexes bearing carboxylate ligands such as $Rh_2(DOSP)_4$ and $Rh_2(PTAD)_4$ were tested in the reaction of **1** using $PhI(OAc)_2$. Under optimized conditions, only moderate yields (50%) of oxazolidinone **(±)-3a** and low enantioselectivities (<20%) were achieved with both catalysts.[17]

Due to the difficulty in finding a compromise between activity and selectivity, we then considered kinetic resolution as an alternative strategy for accessing the desired enantioenriched compounds. In 2006, Birman reported the kinetic resolution of oxazolidinones[18] through an efficient organocatalysed acylation reaction using nucleophilic chiral amidine-based catalysts (ABCs).[19,20] This protocol provided a new approach to the synthesis of enantioenriched oxazolidinones (Scheme 2a). However, the presence of an aryl, alkenyl or ester moiety directly linked to the carbon atom adjacent to the NH group in the oxazolidinone ring was apparently critical for the reaction selectivity (Scheme 2a), driven by cation-π interactions between the thiazolium ring at the acylated catalyst and the π-systems of theses substrates.[18a,21] Based on these structural constraints, very low ee or a total lack of reactivity would be expected in the enantioselective ABC-catalysed acylation of the racemic oxazolidinones obtained in the rhodium-catalysed oxyamination process (Scheme 2b). Moreover, the additional stereocenter present in these compounds could also influence the final outcome of the kinetic resolution.

Despite the distant double bond present at the oxyamination products, we hypothesised that the asymmetric process could be controlled by selecting the protecting group in the hydroxyl function (Scheme 2b). Thus, we undertook a systematic study of different hydroxyl-protecting groups along with other variables affecting the process, such as the catalyst, the acylating agent, the concentration and the temperature.

Additionally, previous computational studies by Birman and coworkers[18a] had proved that cation-π interactions were determinant for the control of the enantioselectivity of the process (Scheme 2a), and therefore we also applied them to analyse the results obtained from our alkenyl oxazolidinones. Computational chemistry has indeed demonstrated to be very convenient to construct useful models to understand the factors that affect organocatalytic reactions in terms of the chemo-, regio- or enantioselectivity.[22] Specifically, density functional theory has been a widely used method in organocatalytic processes such as in cycloadditions,[23] in iodine(III)-mediated reactions[24] and in photoorgano-catalysis.[25]



conditions	yield (dr a:b)				
a	**91%** (66:34)	**(±)-2a**	R=Bz	**(±)-2b**	R=Bz
a	**87%** (75:25)	**(±)-3a**	R=Ac	**(±)-3b**	R=Ac
a	**89%** (91:9)	**(±)-4a**	R=Piv	**(±)-4b**	R=Piv
b	i.ii.**60%** iii.**60%**	**(±)-5**	R=*p*-MeO-Bz		
c	i.ii.**70%**	**(±)-6**	R=Me		

a) $Rh_2(OAc)_4$, $PhI(OR)_2$, Cs_2CO_3. b) i. PhIO, 4Å M.S. ii. H_2O. iii. *p*-MeO-BzCl, py. c) i. PhIO, 4Å M.S. ii. MeOH.

Scheme 3. Preparation of the oxyamination products.

To confirm the previous hypothesis, compounds bearing protecting groups with aromatic rings (**(±)-2a** and **(±)-5**), carbonyl groups (**(±)-2a-5**), or a simple methyl moiety (**(±)-6**) were prepared (Scheme 3). Derivatives **(±)-2a-4a** bearing Bz, Ac, Piv protecting groups were synthesised from carbamate **1**, $Rh_2(OAc)_4$ catalyst and the appropriate $PhI(OR)_2$ reagent under the optimised reaction conditions for a S_N2 aziridine opening. In this case, catalyst and base play a determining role in the efficiency and selectivity (S_N2 versus S_N2') of the oxyamination reaction. [11] Alternatively, PhIO mediated intramolecular aziridination of carbamate **1** was applied for the preparation of compounds **(±)-5** and **(±)-6**, using respectively a mixture of water in acetonitrile or methanol as nucleophiles for the ring opening step. Final esterification of the hydroxyl substituted intermediate with *p*-MeOBzCl rendered oxazolidinone **(±)-5** in good yields.

The role of the acylating agent on the kinetic resolution was initially studied. For this purpose, oxazolidinone **(±)-2a** was selected as model substrate since its benzoate group was anticipated to favour cation-π interactions. Therefore, this substrate was submitted to kinetic resolution conditions, in the presence of 2 mol% of (*R*)-BTM catalyst, 75 mol% of acylating agent, 75 mol% of DIPEA, Na_2SO_4 and using chloroform as solvent (0.2 M respect to the substrate).[26] The addition of DIPEA was found to be crucial to scavenge the acid generated that could reduce catalyst activity. Along these lines, a desiccating agent (Na_2SO_4) was necessary since water could react with the highly electrophilic *N*-acyliminium intermediate.

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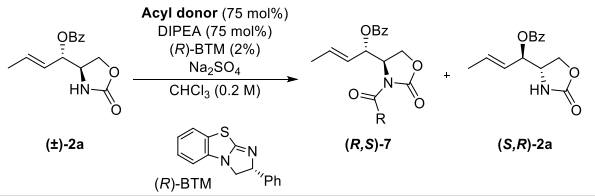
Table 1. Kinetic resolution of **(±)-2a**. Optimisation of the acylating agent.[a]



Entry	Acyl donor	T (ºC)	Conversion (%)[b]	*ee* (P/SM)[c]	Selectivity (*s*)
1[d]	$(Boc)_2O$	20	0	--	--
2	BzCl	20	<5	--	--
3	$(^iPrCO)_2O$	0	47	92/80	59
4	$(^tBuCO)_2O$	0	28	90/35	27

[a] Na_2SO_4 (100 mg per 0.1 mmol of substrate). [b] Determined by ^1H NMR spectroscopy. [c] *ee* (P/SM): product/starting material *ee* ratio. Enantiomeric excess was determined by chiral HPLC (See SI). [d] 4 mol% of (*R*)-BTM was used.

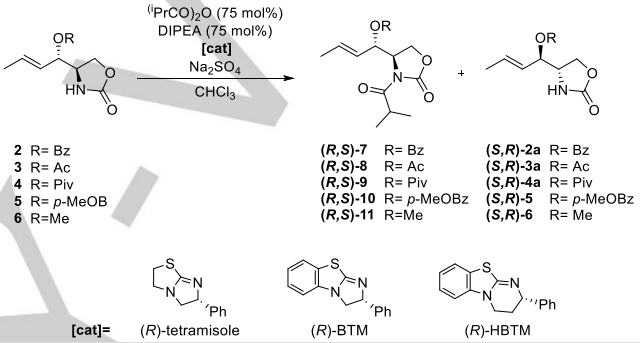
The use of $(Boc)_2O$ did not produce any conversion (Table 1, entry 1).[18b] Likewise, benzoyl chloride failed to give any conversion (Table 1, entry 2), probably due to the nucleophilicity of the chloride released which can interact with the chiral acylating intermediate. As expected, acid anhydrides demonstrated to be active acylating agents for our system. In particular, isobutyric anhydride resulted the best option, providing compound (*R,S*)-**7** in good yield and high selectivity, being even superior to the larger pivalic anhydride (Table 1, entries 3 *vs*. 4). Interestingly, despite the presence of a sp^3 carbon neighbouring the oxazolidinone ring, reaction conversions and enantioselectivities for the acylated product were good.

The influence of the catalyst loading, reaction concentration, temperature, protecting group and catalyst type were then analysed (Table 2). At first sight, it appears that catalyst loading, temperature and concentration do not have a strong influence on the reaction outcome. Looking into more detail, dilution from 0.2 M to 0.1 M produced a considerable decrease in both the activity and enantioselectivity when the reaction was carried out at room temperature (Table 2, entries 1 *vs*. 2). Temperature did not show a clear tendency, the best proving to be 0ºC although with only a very slight improvement comparing with the results obtained at room temperature (Table 2, entry 3). Contrary to what is normally expected in asymmetric processes, further decrease in the temperature to -40ºC resulted in slightly eroded selectivity (Table 2, entries 3 *vs*. 4) which significantly deteriorated when using higher 6 mol% catalyst loading at low temperature (Table 2, entries 4 *vs*. 5).

We next explored the influence of the protecting group and the catalyst type. Interestingly, acetyl derivative **(±)-3a** afforded a similar enantioselectivity than that from the *p*-OMeBz derivative **(±)-5** and close to the previously obtained for the benzoyl derivative **(±)-2a** (Table 2, entries 1, 6 and 8). On the other hand, pivaloyl derivative **(±)-4a** provided lower selectivity (Table 2, entry 7). However, when the hydroxyl moiety was protected as a methyl ether, no reaction was observed after 24h stirring under the standard conditions (Table 2, entry 9). These results confirmed that the efficiency of the kinetic resolution was controlled by the acyl protecting group at the additional stereocentre.[27]

Moreover, the use of different catalysts was studied. Apart from BTM, two other catalysts with a related chemical structure, tetramisole and HBTM, were tested. HBTM is the ring-expanded version of BTM and has been reported to provide an inverse pattern of selectivities in the kinetic resolution of alcohols.[28] Thus, whereas BTM gives high selectivities when the π-system is located α to a nucleophilic atom, HBTM presents better results for substrates bearing the π system at β position. Disappointingly, tetramisole only provided 10% of conversion after 21 hours (Table 1, entry 10), whereas HBTM did not show any improvement in comparison with BTM but actually resulted less effective than expected with a selectivity factor of 18 (Table 1, entry 11).

Table 2. Kinetic resolution of **(±)-2a-6**. Optimisation of the reaction conditions, protecting group and catalyst.[a]



Entry	SM	Cat (mol%)	Time (h)	Temp (ºC)	Conv (%)[b]	*ee*[c] (P/SM)	(s)
1	**2a**	BTM (4)	4	20	43	94/72	70
2[d]	**2a**	BTM (4)	10	20	37	93/55	48
3	**2a**	BTM (4)	4	0	48	93/85	75
4	**2a**	BTM (4)	21	-40	45	92/76	55
5	**2a**	BTM (6)	21	-40	55	80/97	37
6	**3a**	BTM (4)	5	20	46	92/79	60
7	**4a**	BTM (4)	5.5	20	42	89/65	35
8	**5**	BTM (4)	4	20	46	91/79	50
9	**6**	BTM (4)	24	20	--	--	--
10	**2a**	Tetramisole (4)	21	20	10	--	--
11	**2a**	HBTM (4)	32	20	26	86/31	18
12[e]	**2a**	BTM (4)	4	20	43	96/73	108

[a] Na_2SO_4 (100 mg per 0.1 mmol of substrate). [b] Determined by ^1H NMR spectroscopy. [c] *ee* (P/SM): product/starting material *ee* ratio. Enantiomeric excess was determined by chiral HPLC (See SI). [d] Concentration 0.1 M. [e] BTM catalyst was recrystallised three times before being used.

The use of a catalyst batch with recrystallised material rendered the acylated oxazolidinone **(*R,S*)-7** in a slightly improved

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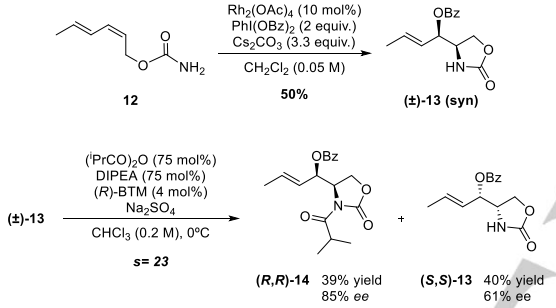
enantioselectivity (96% *ee*) achieving a selectivity factor of 108 (Table 2, entry 12 *vs.* entry 1). Absolute configuration of compound **(*R*,*S*)-7** was assigned by analogy with the acylated oxazolidinone **(*R*,*S*)-18** (See Scheme 7).

We next explored the sequential oxyamination/kinetic resolution protocol for carbamate **12**, with a *Z* configuration at the reactive double bond adjacent to the carbamate moiety. Thus, compound **12** was treated under the optimized aziridination/ring-opening conditions, using $PhI(OBz)_2$ to afford compound **(±)-13** in 50% yield, which in turn was submitted to (*R*)-BTM catalysed kinetic resolution (Scheme 4). The reaction rendered the acylated product **(*R*,*R*)-14** in 39% yield and 85% *ee*, while the starting material was recovered in 40% yield and 61% *ee*, with an *s*-factor of 23. The absolute configuration of compound **(*S*,*S*)-13** was assigned by comparison of its HPLC traces with the same product prepared from Garner's aldehyde applying a stereospecific synthetic route (See supporting information).[29,30] These results confirmed that the configuration of the carbon atom bearing the amino function determines the enantiomer being acylated, for a specific catalysts enantiomer, whereas the adjacent stereocenter has little influence on the final outcome of the kinetic resolution process.



Scheme 4. Synthesis and KR of *syn*-oxazolidinone **(±)-13**.

We next analysed computationally through DFT calculations with the M06-2X functional the origin of the efficient performance of alkenyl oxazolidinones **(±)-2a**-**5** in kinetic resolution. We used a similar treatment to that previously applied by Houk and co-workers for the identification of the important role of cation-π interactions in the efficiency of related systems (Scheme 2a). We evaluated the corresponding diastereomeric transition states starting from substrate **(±)-2a** (in *anti* configuration) and substrate **(±)-13** (in *syn* configuration). Experimentally, substrate **(±)-2a** is more efficient for kinetic resolution than substrate **(±)-13** (s_{exp} = 108 in **(±)-2a** *vs* s_{exp} = 23 in **(±)-13**), and both favour the same isomer.

We report here the key transition states for C-N bond formation from the lactim isomers of our systems (an extended discussion on the lactim-lactam tautomerism is supplied in the Supporting Information). We explored a variety of conformers for the diastereomeric transition states associated to compound **(±)-2a** and the most stable ones are depicted in Figure 1. The energy difference between the **TS-(*R*,*S*)-2a** and **TS-(*S*,*R*)-2a** structures is 4.7 kcal/mol. Despite the computed value overestimates the experimental result (the reported s_{exp}= 108 corresponds to a ΔΔG of 2.8 kcal/mol) the trend is clearly reproduced.

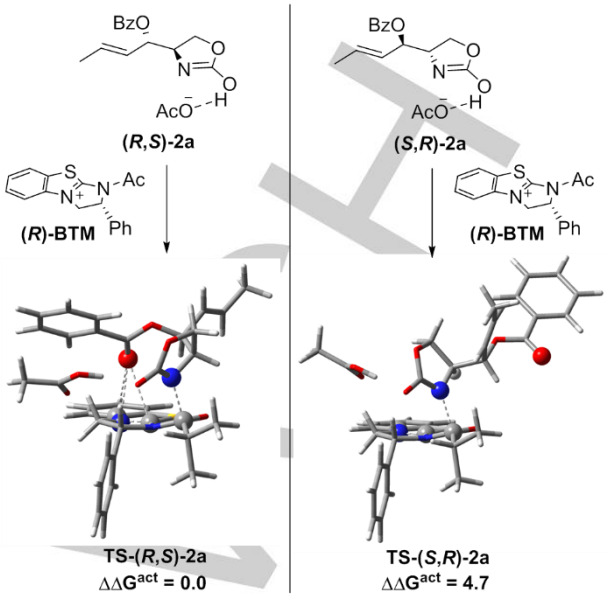


Figure 1. 3D structures of the diasteromeric transition state of N-acylation of compound **(±)-2a** by (*R*)-BTM-Ac catalyst. Free energies in kcal/mol.

Several structural factors in the systems shown in Figure 1 deserve comment. Hydrogen bond interactions between the catalyst, hydroxyl group of the lactim and the acetate play an important role in the transition state. The acetate group in particular is assisting the C-N bond formation by the concerted deprotonation of the O-H moiety in the lactim. These hydrogen bonds are nevertheless quite similar in both transition sates. The main difference between **TS-(*R*,*S*)-2a** and **TS-(*S*,*R*)-2a** is in the interactions of the chain attached to the oxazolidinone ring. In **TS-(*R*,*S*)-2a**, the favoured conformation has the carbonyl group of the benzoate group pointing directly to the cationic BTM ring. The cation-carbonyl distance is between 2.75 and 2.90 Å, stabilizing this transition state respect to **TS-(*S*,*R*)-2a**, where those interactions cannot take place due to the orientation of the side chain away from the catalyst.

We repeated the same calculations for the transition states associated to the *syn* reactant **(±)-13.** The corresponding structures are shown in the Supporting Information (Figure S2). The favoured structure is **TS-(*R*,*R*)-13**, 2.1 kcal/mol below **TS-(*S*,*S*)-13**, again in agreement with the experimental information. In this case, the energy is in better quantitative agreement with the experimental *s* value of 23, associated to ΔΔG of 1.9 kcal/mol. Again, the key interaction is the cation-carbonyl interaction, demonstrating that the stereogenic center of the side chain plays a minor effect in the enantiodifferentiation. Both of the substrates we have considered, **(*R*,*S*)-2a** and **(*R*,*R*)-13**, can reach a stable conformation with the C=O-cation interaction mentioned above.

Finally, in order to illustrate the usefulness of the developed oxyamination/kinetic resolution protocol, we applied it to the enantioselective synthesis of sphingolipid analogues. Two different strategies were envisioned for this purpose: a) sequential oxyamination/kinetic resolution of long-chain dienyl carbamate **16** and b) cross metathesis using enantioenriched product **(*R*,*S*)-7** arising from kinetic resolution as starting material. Thus, carbamate **16**, which was prepared from dienol **15**,[13a] was treated with $PhI(OBz)_2$ using Cs_2CO_3 as base and $Rh_2(OAc)_4$ as catalyst to render oxazolidinone **(±)-17** as a single regioisomer in 62% yield (Scheme 5a). Compound **(±)-17** was then submitted to kinetic resolution conditions furnishing acylated oxazolidinone

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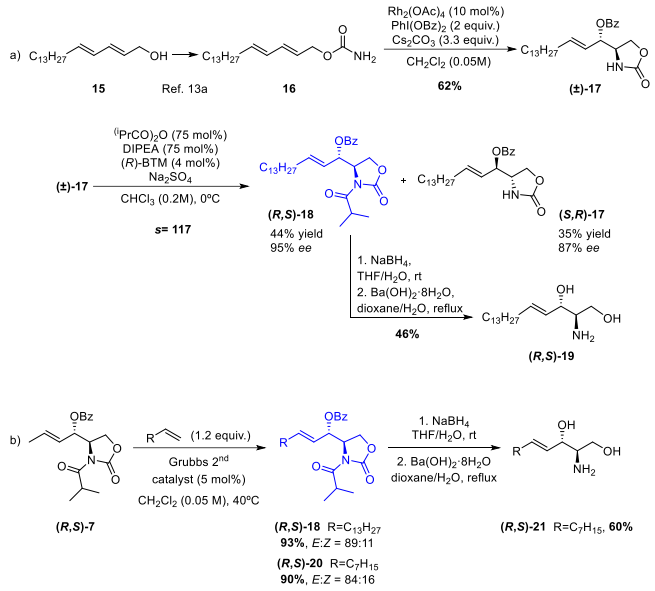
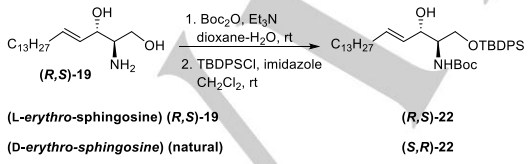
(*R,S*)-18 in 44% yield and 95% *ee* along with enantioenriched starting material (***S,R***)-**17** in 35% yield and 87% *ee* (s-factor of 117).[31] Final deprotection of intermediate **(*R,S*)-18** gave access to L-*erythro*-sphingosine **(*R,S*)-19**.



Scheme 5. a) Enantioselective synthesis of **(*R,S*)-19** (L-*erythro*-sphingosine) via sequential oxyamination/kinetic resolution. b) Enantioselective synthesis of **(*R,S*)-18** (L-*erythro*-sphingosine precursor) and **(*R,S*)-21** (clavaminol H derivative) via cross metathesis.

Alternatively, double bond functionalisation of acylated oxazolidinone **(*R,S*)-7** under optimised cross metathesis conditions with commercially available 1-pentadecene and 1-nonene rendered intermediates **(*R,S*)-18** and **(*R,S*)-20** in high yields and good *E*:*Z* ratios (Scheme 5b. See supporting information for the optimisation study).[32] Compound **(*R,S*)-20** was finally deprotected by reaction with $NaBH_4$ and $Ba(OH)_2{\cdot}8H_2O$ to obtain clavaminol H derivative **(*R,S*)-21**.

The absolute configuration of compound (***R,S***)-**19** was assigned by comparison of the HPLC traces recorded under identical conditions of derivatives (***R,S***)-**22** and (***S,R***)-**22,** obtained from (***R,S***)-**19** and natural commercially available (*S,R*)-sphingosine, respectively (Scheme 6). The results confirmed that the (*R*)-BTM catalysed kinetic resolution of oxazolidinone **(±)-17** afforded the synthetic sphingosine **(*R,S*)-19** with opposite configuration than that of the natural occurring product (See supporting information).



Scheme 6. Assignment of the absolute configuration of the synthetic sphingosine **(*R,S*)-19**.

In conclusion, oxazolidinones resulting from the oxyamination of dienyl carbamates, such as compounds **(±)-2a-5**, are good substrates for the acylation-kinetic resolution process using the amidine-based Birman's catalyst. The efficiency of this kinetic resolution is determined by the presence of an appropriate protecting group in the hydroxyl moiety. Acyl protecting groups are in general suitable due to their stabilization of the favoured transition state by C=O-cation interactions. Among them, benzoyl group is the one providing higher selectivities. Moreover, in the presence of (*R*)-BTM catalyst, compounds with *E* configuration afforded better *s* values that the related *Z* analogues. Combining regio- and steroeselective intramolecular rhodium-catalysed aziridination of dienyl carbamates with organocatalysed kinetic resolution of intermediate oxazolidinones, it was possible to obtaining aminodiols in high enantioselectivities. The usefulness of this methodology was demonstrated by preparing enantioenriched L-*erythro*-sphingosine **(*R,S*)-19** from dienol **15** in five steps and clavaminol H derivative **(*R,S*)-21** from commercially available (2*E*,4*E*)-hexa-2,4-dien-1-ol in six steps. These results constitute a new strategy for accessing enantioenriched aminoalcohols derived from oxyamination processes and expand the applicability of ABC's organocatalysts.

Experimental Section

General procedure for the conversion of allylic dienols to carbamates (carbamoylation).[33] A solution of trichloroacetyl isocyanate (TAI) (1.05 mmol) in dry benzene (1 mL / mmol dienol) was added to a solution of dienol (1.00 mmol) in dry dichloromethane (2 mL / mmol dienol). The mixture was left at room temperature until TLC showed complete consumption of the starting dienol. Then a 20 mol% solution of K_2CO_3 in methanol (3 mL / mmol dienol) was added and the mixture was stirred at room temperature for 3 hours. After solvent evaporation, the residue was dissolved in a 1:1 mixture of dichloromethane and brine. The aqueous phase was extracted with dichloromethane and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure.

General procedure for the tandem intramolecular aziridination-ring opening of allyl carbamates.[11] The corresponding carbamate (0.10 mmol), oxidizing agent $PhI(OR)_2$ (0.20 mmol), oven-dried MgO (0.33 mmol) and rhodium (II) dimer $Rh_2(OAc)_4$ (0.01 mmol) were placed in a 10 mL flame dried Schlenk flask. Then CH_2Cl_2 (2 mL) was added and the mixture was stirred at room temperature until TLC showed complete consumption of the starting material. The reaction crude was initially purified through a short silicagel column (2-3 cm), washing with hexanes to 50:50 AcOEt/hexanes to afford an essentially pure mixture of regioisomers. Separation of isomers was achieved by column chromatography, although yields dropped significantly after prolonged contact with silicagel.

General procedure for one-pot PhIO mediated Aziridination/Ring-Opening. A flame dried Schlenk flask containing a magnetic stirring bar was charged with activated 4Å M.S. (100 mg / 0.1 mmol carbamate) in distilled CH_2Cl_2 (0.04M) under argon atmosphere. Dienyl carbamate (1.0 mmol) and PhIO (2.0 mmol) were added and the heterogeneous mixture was stirred at 35ºC until TLC showed complete consumption of the starting material. Nucleophile was then added and the reaction mixture was stirred overnight. The crude solution was filtered over celite, abundantly washed with CH_2Cl_2 and concentrated under reduced pressure. The reaction crude was purified through a short column chromatography (2-3 cm) in order to avoid product decomposition under prolonged contact with silicagel.

General procedure for the BTM-catalysed kinetic resolution of oxazolidinones with isobutyric anhydride. The reactions were set at the globe box. The catalyst was used within a solution which was prepared by dissolving (*R*)-BTM (10.1 mg, 0.04 mmol) and DIPEA (131 µL, 0.75 mmol) in $CHCl_3$ (4.9 mL). One dram vial was charged with the oxazolidinone substrate (0.10 mmol) and 0.5 mL of the catalyst solution. Then 100 mg of Na_2SO_4 were added and the reaction mixture was magnetically stirred for 5 min before being treated with isobutyric anhydride (0.075 mmol). The reaction mixture was kept under stirring and followed by ^1H NMR. Methanol was finally added to quench the reaction.

General procedure for the *N*-acylation of racemic oxazolidinones with isobutyric anhydride.[34] Oxazolidinone (0.10 mmol) was dissolved in CH_2Cl_2 (0.1 M) at room temperature under argon atmosphere. Et_3N (0.10 mmol) was then added and the solution was cooled to 0ºC. Stirring was continued for approximately 20 min and DMAP (2.5 mol%) and ($^iPrCO_2$)O

(0.11 mmol) were subsequently added. The resulting mixture was kept at 0ºC for one hour and then warmed to room temperature. After completion, the crude was concentrated under reduced pressure.

General procedure for the cross metathesis of alkenyl oxazolidinones with terminal olefins. A two-neck round-bottom flask fitted with a reflux condenser was charged with a solution of alkenyl oxazolidinone (0.10 mmol) in dry dichloromethane (0.05 M). Terminal olefin (0.12 mmol) and Grubbs catalyst 2nd generation (5 mol%) were then added and the reaction mixture was stirred at 40ºC for 24 h. After completion, the crude was concentrated under reduced pressure.

Computational Details. All the calculations were carried out using Gaussian09 (Rev. D01)[35] at the M062X level of theory.[36] All the structures were optimized in solution using the SMD implicit solvation method,[37] with chloroform as solvent (ε = 4.7113). For optimizations and frequency calculations we used the standard basis set 6-31G(d).[38] Potential energies were further refined using the basis set 6-311++G(d,p).[39] This methodology has been proved to provide accurate results on similar systems.[40]

All the stationary points were assigned to minima or transition states by frequency analyses (zero imaginary frequencies for minima and one for transition states). All the energies reported in the manuscript are free energies in solution calculated at 298 K and 1 atm in kcal/mol. Due to the flexibility of the system and the importance of conformation analysis in this type of calculations,[41] a conformational analysis of key transition states were done. In addition, ^{i}PrCOO^{-} was replaced by AcO^{-} to simplify the conformational search, as it was done in previous studies.[40] A data set collection of computational results is available in IoChem-BD repository.[42]

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Conflict of interest

The authors declare no conflict of interest

Keywords: kinetic resolution • organocatalysis • ABC catalysts • oxyamination • enantioselectivity

[1] S. T. Pruett, A. Bushnev, K. Hagedorn, M. Adiga, C. A. Haynes, M. C. Sullards, D. C. Liotta, A. H. Merrill *Jr, Lipid Res.* **2008**, *49*, 1621.
[2] Review de clavavinol a) T. V. Kumar- Reddy, A. Jyotsna, B. L. A. Prabhavathi-Devi, R. B. N. Prasad, Y. Poornachandra, C. G. Kumar, *Eur. J. Med. Chem.* **2016**, *120*, 86. b) A. Aiello, E. Fattorusso, A. Giordano, M. Menna, C. Navarrete, E. Muñoz, *Tetrahedron,* **2009**, *65*, 4384.
[3] a) A. Dyckman *J. Med. Chem.* **2017**, doi: 10.1021/acs.jmedchem.6b01575. b) M. Wymann, R.; Schneiter, *Nat. Rev. Mol. Cell Biol.* **2008**, *9*, 162. c) Y. A. Hannun, R. M. Bell, *Science* **1989**, *243*, 500. d) Y. A. Hannun, in: Sphingolipid-mediated Signal Transduction, Y. A. Hannun (Ed.), R.G. Landes Comp. and Chapman & Hall, New York, **1997**.
[4] a) The Role of Sphingolipids in Cancer Development and Therapy. *Adv. Cancer Res.*, vol 117, J. S. Norris,. Ed., Academic Press, **2013**. b) J. Newton, S. Lima, M. Maceyka, S. Spiegel, *Exp. Cell Res.* **2015**, *333*, 195. c) C. Huang, C. Freter *Int. J. Mol. Sci.* **2015**, *16*, 924.
[5] L. M. Healy, J. P. Antel, *Curr. Drug Targets* **2016**, *17*, 1841.
[6] a) L. Cavone, R. Felici, A. Lapucci, D. Buonvicino, S. Pratesi, M. Muzzi, B. Hakiki, L. Maggi, B. Peruzzi, R. Caporale, F. Annunciato, M. P. Amato, A. Chiarugi *Brain Behav. Immun.* **2015**, *50*, 78. b) S. Ladisch, R. Li, E. Olson, *Proc. Natl. Acad. Sci. U. S. A.,***1994**, *91*, 1974.
[7] a) Y. Gao, X. He, F. Ding, Y. Zhang, *Synthesis*, **2016**, *48*, 4017. b) M. Martinková, J. Gonda, D. Jacková, D. *Tetrahedron: Asymmetry* **2016**, *27*, 1187. b) J. A. Morales-Serna, J. Llaveria, Y. Díaz, M. I. Matheu, S. Castillon, *Curr. Org. Chem.* **2010**, *14*, 2483.
[8] T. J. Donohoe, A. Flores, A. R. Lacy, A. H. Rathi, *Chem. Eur. J.* **2011**, *17*, 58.
[9] D. Leonori, P. H. Seeberger, *Org. Lett.* **2012**, *14*, 4954.
[10] a) T. J. Donohoe, C. J. R. Bataille, W. Gattrell, J. Kloesges, E. Rossignol, *Org. Lett.* **2007**, *9*, 1725. b) T. J. Donohoe, P. D. Johnson, M. Helliwell, M. Keenan, *Chem. Commun.* **2001**, 2078.
[11] J. Guasch, Y. Díaz, M. I. Matheu, S. Castillon, *Chem. Commun.* **2014**, *50*, 7344.
[12] a) H. Ohno, *Chem. Rev.* **2014**, *114, 7784*. b) G. Deguirez, U. Pons, P. Dauban, *Angew. Chem. Int. Ed.* **2012**, *51*, 7384. c) H. Pellissier, *Tetrahedron* **2010**, *66,* 1509. d) J. Ciesielsky, G. Dequirez, P. Retailleau, V. Gandon, P. Dauban, *Chem. Eur. J.* **2016**, *22*, 9338. e) W. P. Unsworth, S. G. Lamont, J. Robertson, *Tetrahedron* **2014**, *70*, 7388. f) W. P. Unsworth, N. Clark, T. O. Ronson, K. Stevens, A. L. Thompson, S. G. Lamont, J Robertson, Chem. Commun. **2014**, *50*, 11393. g) R. Bodner, B. K. Marcellino, A. Severino, A. L. Smenton, C. M. Rojas *J. Org. Chem.* **2005**, *70*, 3988. h) A. Padwa, A. C, Flick, C. A. Leverett, T. Stengel, *J. Org. Chem.* **2004**, *69*, 6377.
[13] For an intermolecular synthesis of vinylaziridines through an intermolecular process see: a) J. Llaveria, A. Beltrán, M. M. Díaz-Requejo, M. I. Matheu, S. Castillon, P. J. Pérez, *Angew. Chem Int. Ed.* **2010**, *49*, 7092. b) J. Llaveria, A. Beltrán, W. M. C. Sameera, A. Locati, M. M. Díaz-Requejo, M. I Matheu, S. Castillon, F. Maseras, P. J. Pérez, *J. Am. Chem. Soc.* **2014**, *136*, 5342.
[14] For a silver-catalyzed asymmetric aziridination of homoallyl carbamates see: M. Ju, C. D. Weatherly, I. A. Guzei, J. M. Schomaker, *Angew. Chem. Int. Ed.* **2017**, *56*, 9944.
[15] For reviews see: a) P. Doyle *J. Org. Chem.* **2006**, *71*, 9253. b) J. Hansen, H. M. L. Davies, *Coord. Chem. Rev.* **2008**, *252*, 545. c) M. El-Deftar, R. G. Adly, M. G. Gardiner, A. Chanem, *Curr. Org. Chem.* **2012**, *16*, 1808. d) F. G. Adly, A. Ghanem, *Chirality* **2014**, *26*, 692. e) Y. Deng, H. Qiu, H. D. Srinivas, M. P. Doyle, *Curr.Org. Chem.* **2016**, *20*, 61. f) G. Dequirez, V. Pons, Ph. Dauban, *Angew. Chem. Int. Ed.* **2012**, *51*, 7384.
[16] Good enantioselectivities in cyclization of indol containing carbamates have been reported: a) (Rh(II)): S. Sato, M. Shibuya, N. Kanoh, Y. Iwabuchi, *Chem. Commun.* **2009**, 6264. b) (Fe(II)): Y-Q. Zhang, Y-A. Yuan, G-S. Liu, H. Xu. *Org. Lett.* **2013**, *15*, 3910.
[17] Rh(II)-catalyzed asymmetric aziridination of homoallyl carbamates afforded ee<23%. C. J. Hayes, P. W. Beavis, L. A. Humphries, *Chem. Commun.* **2006**, 4501.
[18] a) X. Yang, V. D. Bumbu, Liu, X. Li, H. Jiang, E. W. Uffman, L. Guo, W. Zhang, X. Jiang, K. N. Houk, V. B. Birman, *J. Am. Chem. Soc.* **2012**, *134*, 17605. b) V. B. Birman, H. Jiang, X. Li, L. Guo, E. W. Uffman, *J. Am. Chem. Soc.* **2006**, *128*, 6536.
[19] For a recent review by Birman see: V. B. Birman, *Aldrichimica Acta,* **2016**, *49*, 23.
[20] For more general reviews see: a) P. Somfai, *Angew. Chem. Int. Ed.* **1997**, *36*, 2731. b) S. France, D. J. Guerin, S. J. Miller, T. Lectka, T. *Chem. Rev.* **2003**, *103*, 2985. c) E. Vedejs, M. Jure, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 3974. d) J. E. Taylor, S. D. Bull, J. M. Williams, *Chem. Soc. Rev.* **2012**, *41*, 2109.
[21] X. Li, P. Liu, K. N. Houk, V. B. Birman, *J. Am. Chem. Soc.* **2008**, *130*, 13836.
[22] For reviews see: a) Q. Peng, F. Duarte, R. S. Paton, *Chem. Soc. Rev.* **2016**, *45*, 6093. b) P. H.-Y. Cheong, C. Y. Legault, J. M. Um, N. Çelebi-Ölçum, K. N. Houk, *Chem. Rev.* **2011**, *111*, 5042.
[23] C. Liu, M. Besora, F. Maseras, *Chem. Asian. J.* **2016**, *11*, 411.
[24] I. Funes-Ardoiz, W. M. C. Sameera, R. M. Romero, C. Martínez, J. A. Souto, D. Sampedro, K. Muñiz, F. Maseras, *Chem. Eur. J.* **2016**, *22*, 7545.
[25] L. Dell'Amico, V. M. Fernández-Álvarez, F. Maseras, P. Melchiorre, *Angew. Chem. Int. Ed.* **2017**, *56*, 3304.
[26] a) V. B. Birman, E. W. Uffman, H. Jiang, X. Li, C. J. Kilbane, *J. Am. Chem. Soc.* **2004**, *126*, 12226. b) V. B. Birman, H. Jiang, *Org. Lett.* **2005**, *7*, 3445. c) V. B. Birman, X. Li, *Org. Lett.* **2006**, *8*, 1351.
[27] Kinetic resolution performed on regioisomeric products **2b**-**4b** proceeded with very low conversions.
[28] V. B. Birman, X. Li, *Org. Lett.* **2008**, *10*, 1115.
[29] Leonori, D.; Seeberger, P. H. *Org. Lett.* **2012**, *14*, 4954.
[30] Abad, J. L.; Nieves, I.; Rayo, P.; Casas, J.; Fabriàs, G.; Delgado, A. *J. Org. Chem.* **2013**, *78*, 5858.
[31] Related compounds called ceramides have shown anticancer activity. A. Sing, H-J. Ha, J. Park, H. J. Kim, H. J. Lee, *Bioorg. Med. Chem.* **2011***, 19,* 6174.

10.1002/chem.201705670

[32] a) H. Hasegawa, T. Yamamoto, S. Hatano, T. Hakogi, S. Katsumura, *Chem. Lett.* **2004**, *33*, 1592-1593. b) S. Torssell, P. Somfai, *Org. Biomol. Chem.* **2004**, *2*, 1643-1646.
[33] C. G. Espino, J. Du Bois, *Angew. Chem. Int. Ed.* **2001**, *40,* 598.
[34] C. S. Schindler, P. M. Forster, E. M. Carreira, *Org. Lett.* **2010**, *12*, 4102.
[35] Gaussian 09, Revision D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.
[36] Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215.
[37] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B*, **2009**, *113*, 6378.
[38] a) M. M. Francl, W. J. Pietro, W. J. Hehre, J. S. Binkley, M. S. Gor)don, D. J. DeFrees, J. A. Pople, *J. Chem. Phys.* **1982**, *77*, 3654-3665. b) P. C. Hariharan, J. A. Pople, *Theoret. Chim. Acta* **1973**, *28*, 213-222. c) W. J. Hehre, R. Ditchfield, J. A. Pople, *J. Chem. Phys.* **1972**, *56*, 2257-2261.
[39] R. Krishnan, J.S. Binkley, R. Seeger, J.A. Pople, *J. Chem. Phys.* **1980**, *72*, 650-654.
[40] P. Liu, X. Yang, V. B. Birman, K. N. Houk, *Org. Lett.* **2012**, *14*, 3288.
[41] M. Besora, A. A. C. Braga, G. Ujaque, F. Maseras, A. Lledós, *Theor. Chem. Acc.* **2011**, *128*, 639.
[42] M. Álvarez-Moreno, C. de Graaf, N. López, F. Maseras, J. M. Poblet, C. Bo, *J. Chem. Inf. Model.* **2015**, *55*, 95-103.

10.1002/chem.201705670

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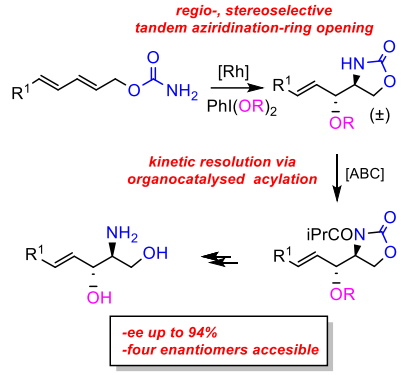	Tandem regio- and steroeselective intramolecular rhodium-catalysed aziridination of dienyl carbamates/ opening followed by kinetic resolution via ABC-catalysed acylation of the oxazolidinones obtained, and deprotection, allows obtaining aminodiols with high enantioselectivity. This kinetic resolution process overcomes reported structural limitations. The efficiency of this methodology was demonstrated by preparing enantioenriched (*R,S*)-sphingosine	*ABC KR of oxazalidinones* *J. Guasch, I. Giménez, I. Funes-Ardoiz, M. Bernús, M.I. Matheu, F. Maseras, S. Castillón,* Y. Díaz** **Enantioselective Synthesis of Aminodiols by Sequential Rh-Catalysed Oxyamination/ Kinetic Resolution. Expanding the Substrate Scope of Amidine- Based Catalysis**

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